
# *CBER Centennial: Issues in Therapeutics Research*

Jay P. Siegel, M.D., FACP, Director
Office of Therapeutics Research and Review
Center for Biologics Evaluation & Research, FDA


# *OTRR Regulates Products of Emerging/Evolving Technologies*

- Monoclonal antibodies
- Recombinant proteins
- Gene therapy
- Cell and tissue therapies

OTRR

# *Monoclonal antibodies*

- Rapidly evolving production, e.g., phage libraries, transgenic plants
- Engineering, e.g.,
  - Humanization
  - Chelation:  radioimmunotherapy
  - Replacement of variable regions with biological receptors
  - Immunotoxins.

OTRR

# *Recombinant proteins*

- Rapidly evolving production, e.g.
  - Transgenic plants, animals
  - PEGylation, mutations
  - Serum free production
  - Protein free formulation

OTRR

## *New therapeutic targets, e.g.,*

- Angiogenesis
- Tolerance induction
- Signal transduction
- Oncogenes, growth factor receptors
- Protection from radiation injury
- Anti-bioterrorism agents


# *Gene therapy*

- Newly developed vectors
- Targeting strategies
- Regulating strategies

OTRR

# *Cell and tissue therapies, e..g.*

- Hematopoietic stem cells
- Embryonic stem cells
- Expanded lymphocytes
- Assisted reproductive technologies
- Tissue engineering
- Pancreatic islet cells
- Hepatocytes
- Cartilage
- Xenotransplantation


# *Complexity of reviewing products of new technologies is often rather high*

- More manufacturing concerns and issues
  - e.g., comparability, manufacturing changes
  - Less experience regarding process concerns/controls
- New indications and modalities
  - Lacking validated animal models
  - Lacking validated endpoints
  - Less prior advisory committee guidance
  - No track record of what works and what does not
  - Harder to predict long term safety concerns

# *Regulation of new and evolving technologies*

- Requires extensive state-of-the-art scientific input for:
  - Applications review
  - Developing regulatory frameworks
  - Providing scientific and regulatory guidance


# *Science-based regulation of new and evolving technologies*

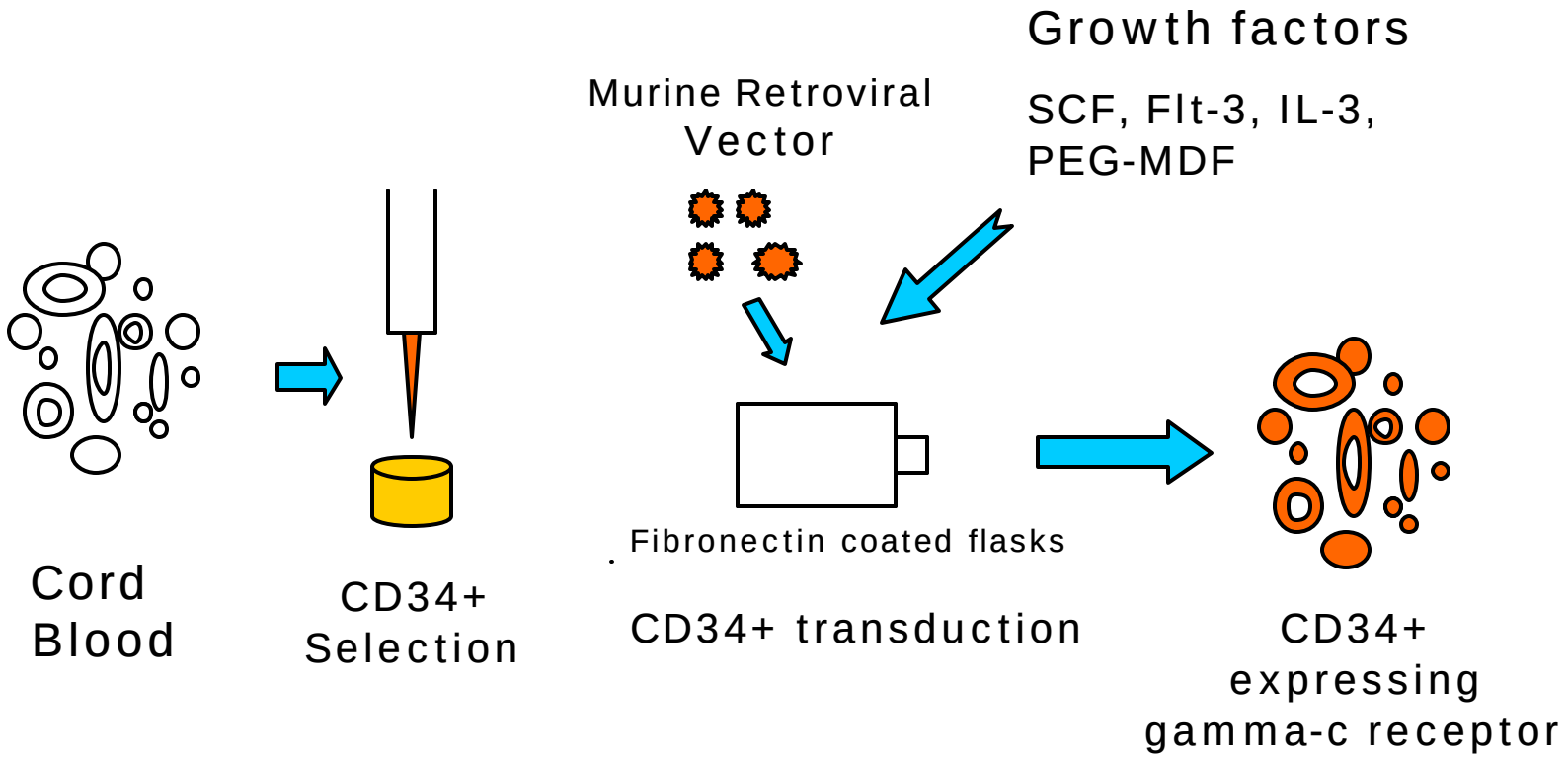
- Broad Outreach for Scientific Input
  - Workshops, hearings, advisory committee meetings, scientific meetings, international meetings, draft guidance for comment
- In-house, state-of-the-art scientific/medical expertise
- Research/reviewers play a key role.
  - To generate critical data
  - To apply state-of-the-art expertise
  - To apply hands-on experience with technologies


# *Selected issues in biotechnology therapeutics development currently addressed by OTRR, CBER*

- Developing regulatory frameworks
  - definitions, regulations, guidance, etc.
  - xenotransplantation, cell/tissue therapies, etc.
- Concomitant development of targeted therapies and diagnostics (e.g., proteomic or genomic)
- Immunogenicity
- Product consistency, manufacturing changes

# Complexity of (a) Gene Therapy Product

Ex Vivo Transduced CD34+ Cells
Expressing GammaC-R for X-SCID



OTRR

# *Policy and guidance development*

- Gene Therapy
- Cell Therapy and Tissues
- Xenotransplantation
- Recombinant Proteins
- Monoclonal Antibodies
- Transgenic Plants
- Clinical Data Requirements - General
- Clinical Data Requirements - Disease Specific

# *Immunogenicity*

- Loss of efficacy, change in PK, serum sickness, neutralization of endogenous homologue (tPO)
- The EPO story
  - 1998:  Eprex mfg changes approved outside U.S.
  - Includes new HSA free formulation
  - Pure Red Cell Aplasia
  - Neutralizing antibodies to endogenous erythropoietin
- Some suggested potential risk factors
  - Differences in structure or presentation, denaturation, microaggregation, subcutaneous use, competence of host, intermittent use.

OTRR

# *Comparability, manufacturing changes*

- Biological products are difficult to manufacture consistently and difficult to characterize fully.
- The ability to produce a consistent, quality product is often the rate-limiting step in getting to market.
- Changes in production or formulation have often, unexpectedly, changed products.
  - early process changes: cell bank, fermentation
  - new facilities, suppliers, processes
  - formulation changes
    - pre-filled syringe (changes in: PK, stability, microaggregates)

# *Proteomics / Genomics*

- Impact on therapeutics development and regulation:
  - New therapeutic targets
  - New diagnostics, subpopulations, indications
  - New markers for toxicity
  - New endpoints for efficacy
  - New endpoints for potency
  - New assays for product quality, e.g., identity, purity

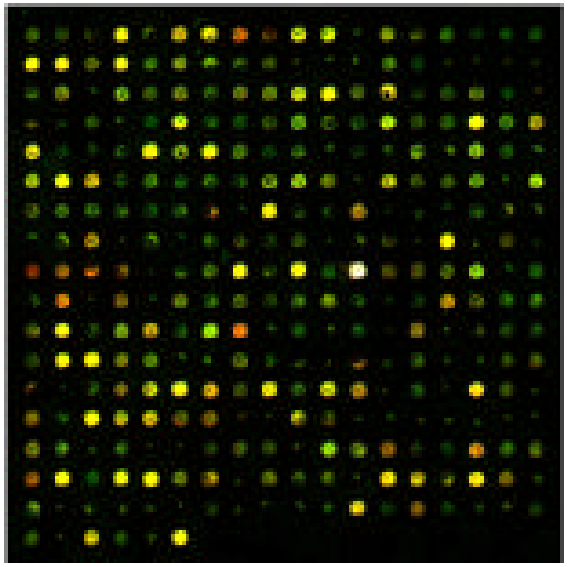
# *Regulatory research proteomics and genomics*

- Proteomics
  - Identification of early serologic markers of drug induced cardiotoxicity
  - Evaluating use of proteomic tools to evaluate product purity and consistency
- Genomics
  - Genomic characterization of cell substrates.

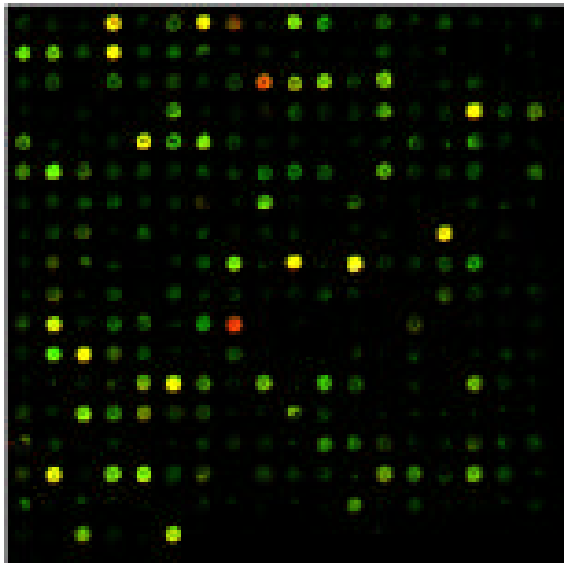
# *Quality assessment of cell substrates by cDNA microarray*

## *(293 embryonic kidney cell line used to produce Ad vector)*

**90% Confluence**



**Over confluence**



**Up regulation of stress-related genes in over confluent cells:**

P4HA1, procollagen-proline; TXNIP, thioredoxin interacting protein; ALDOA, aldolase A; ENO2, enolase 2; LDGA, lactate dehydrogenase A

OTRR

# *Retroviral safety*

- Retroviruses are present in many mammalian producer lines and cellular products
- Species-restricted viruses could develop human tropism and pathogenicity from
  - mutation, recombination, phenotypic mixing
- CBER research
  - Clearance of murine retrovirus in monoclonal antibody production
  - Porcine endogenous retroviruses (PERV) in xenotransplantation

# *PERV research*

- Risk assessment
  - infectious PERV can be isolated from activated pig peripheral blood mononuclear cells and plasma.
  - studies into factors regulating infectivity.
- PERV assessment tools
  - Sensitive, quantitative, specific PCR assays
  - Optimized reverse transcriptase detection
    - Conventional, PCR-based (TM-PERT)
  - Pseudotype assays for virus infectivity
  - Western blot for detection of viral proteins or antibodies to PERV

# *Clinical research*

- Division of Clinical Trial Design & Analysis: Experts in medicine and the science of clinical research have greatly facilitated clinical product development in many areas.
  - Sepsis
  - Acute MI
  - Gene therapy / good clinical practices
  - Many others, e.g., rheumatoid arthritis, lupus, coronary interventions, hepatitis C, psoriasis, hematopoietic support and transplantation, Crohn's disease. wound healing.

OTRR

# *Why research-based regulation?*
## *(from CBER Research Oversight Report)*

- 1. Regulators and policy makers require expert knowledge and first hand experience with the latest technology being applied to biological products
- 2. An intramural research program is required to assess risks of new therapies, to develop assays and new approaches to increase efficacy and safety, and reduce risks.
- 3. A strong well maintained intramural research program provides the basis for a climate of science and scientific communication within CBER that enhances the ability of the Agency to recruit and retain high quality scientific staff

# *Why research-based regulation? (cont.)*

- 4. The research program facilitates the ability of CBER to address existing regulatory issues and to anticipate future problems to keep pace with rapidly emerging and complex cutting edge technology.
- 5. The existence of an intramural research program is necessary for CBER to launch a credible emergency response to adventitious agent problems with marketed biologics.
- 6. Research based internal expertise enhances the ability of the Agency to interact productively with sister agencies (both in the US and internationally), academia and industry as a respected knowledgeable and impartial colleague.

# *OTRR, CBER approved products: The Biotechnology Revolution*

- Oncology
  - Herceptin (trastuzumab) breast cancer, ushers in new area of highly targeted therapy
  - Rituxan (ritiximab) targets some lymphomas
  - Zevalin* (ibritumomab tiuxetan), first monoclonal antibody targeted radiotherapy
  - Campath* (alemtuzumab) for CML

# *Biologic Therapeutics Continued*

- Hematopoietic support
  - Several CSFs (Neulasta*: PEG-G-CSF) support WBC production and decrease infection risk
  - Several EPOs (Aranesp*:  darbepoietin) support RBC, treat anemia in cancer, renal failure
  - Hematopoietic stem cell selection devices

# *Biologic Therapeutics Continued*

- Cardiology
  - Fibrinolytics reduce mortality of acute MI
  - ReoPro (abciximab) anti-platelet agent prevents abrupt coronary closure after coronary procedures.
- Infectious Diseases
  - Xigris* (rhAPC): first therapy targeting severe sepsis, reduces mortality in high risk patients
  - IFN alfas (PEG-IFN alpha* / ribavirin): chronic Hepatitis C
  - Synagis:  prevent RSV infections

# *Biologic Therapeutics Continued*

- Pulmonary:  DNase for cystic fibrosis
- Hereditary deficiencies:  IFN gamma for osteopetrosis, CGD
- Gastrointestinal:  Remicade (anti-TNF) - Crohn's Ds.
- Transplantation:  Simulect, Zenapax (anti-IL-2R)
- Hyperuricemia in CA:  Elitek* (Uricase)

# *Biologic Therapeutics Continued*

- Arthritis
  - Remicade (anti-TNF) - RA
  - Enbrel (Fc TNF-R) - RA, JRA, Psoriatic Arthritis
  - Anakinra* (IL-1RA) - RA
- Neurology:
  - Betaseron, Avonex, Rebif* (IFNs beta): Multiple sclerosis
  - tPA for stroke


# *The OTRR, CBER record*

- Science-based regulation of biologic therapeutics at OTRR has played a central role in the development and availability of safe and effective products of biotechnology that are revolutionizing medicine.
- OTRR scientists/physicians work independently of but closely with regulated biotechnology.
  - Extraordinary number of meetings
  - Timely, science based guidance
- OTRR scientists/physicians have provided international leadership in the science-based regulation of biotechnology products.


## *The OTRR, CBER record (continued)*

- The number of new product approvals is increasing.
- Despite the complexity and novelty of biotechnology products, review times and approval times compare favorably with those for other types of drugs.
- Biological therapeutics are often available first in the U.S.
- There has ***never*** been need to recall an OTRR-approved biotechnology drug due to safety concerns.